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Quinoxalin-2-ones Part 5. Synthesis and antimicrobial evaluation of 3-alkyl-, 3-halomethyl- and 3-carboxyethylquinoxaline-2-ones variously substituted on the benzo-moiety

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Dedicated to the memory of Professor Paolo Sanna, died on the 28th March 2002

Abstract

A new series of 3-alkyl-, 3-trifluoromethyl-, 3-carboxyethyl- and 3-bromomethylquinoxaline-2-ones and 2,3-bis(bromomethyl)quinoxalines bearing Cl, CF_3, morpholine on the benzo-moiety, were synthesised and submitted to a preliminary in vitro evaluation for antibacterial and anticandida activities. Results of the screening showed that compounds **9b**, **14b** and **19b** (MIC = 62.5 μg/ml) and **10b** (MIC = 15.6 μg/ml) were the most active against *Vibrio alginolyticus*.
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Keywords: 2-Quinoxalinones; Quinoxalines; Antimicrobial activity

1. Introduction

Interest in the medicinal properties of quinoxalin-2-ones has stimulated our research in this field [1–3]. Recently we reported the synthesis and biological activities of over 120 quinoxalin-2-ones [4–7] and 12 pyrido[2,3-*g*]quinoxalin-2-ones [8]. Among the quinoxalin-2-one series, we have observed that compounds bearing a carboxyethyl at C-3 and a CF_3 group or a morpholine ring in the benzo-moiety were moderately active against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively [4], while those with an ethyl at C-3 and a CF_3 group in the benzo-moiety exhibited activity against *P. aeruginosa* [5]. Introduction of a CH_2Br group at C-3 and a CF_3, or a NO_2 group in the benzo-moiety exhibited activity against *Staphylococcus aureus* and *Candida* spp., respectively [6]. The CF_3 group at both C-3 and the benzo-moiety of quinoxalinones showed to maintain this activity against *C. albicans* and *C. parapsilosis* spp. [6], while a CF_3 group at C-3 and Cl atoms in the benzo-moiety exhibited activity against *S. aureus* [7]. Among the pyrido[2,3-*g*]quinoxalin-2-one series, we have observed that compounds bearing substituents such as a alkyl, CF_3 or CH_2Br group at C-3 or C-2 and Cl atom at C-5 exhibited both antibacterial and anticandida activities [8].

These results prompted us to continue our investigation on quinoxalin-2-ones in order to achieve additional data for a structure-activity relationship study. In this context, in order to evaluate if the concomitant presence of two favourable substituents in the benzo-moiety might improve antimicrobial activity, we have prepared a new series of quinoxalin-2-ones bearing either a chlorine atom or a CF_3 group in the benzo-moiety, or alternatively a chlorine atom and a morpholine ring in 5,6 (or 7,8) positions of quinoxaline nucleus.

Furthermore, we have synthesised the 2,3-bis(bromomethyl)quinoxalines bearing the same substituents as above in the benzo-moiety (Cl, CF_3, morpholine), in

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order to verify if this type of biological activity was maintained or not on the quinoxaline scaffold.

2. Chemistry

The starting diamines **4b**,**c** were commercially available, while **4a** was prepared according to Scheme 1. The quinoxalinones (**6a**, **7a**, **8a**–**b**, **9b**, **10a**–**b**, **11a**, **12a**–**b**, **13a**–**b**, **14a**–b, **15a**–**b**, **16a**–**b** and **17a**) listed in Table 1, were prepared following the procedure depicted in Scheme 2 according to our previous reports [4–7]. The reaction of the diamines **4a**,**b** with the suitable α-ketoesters **5c**–**h** was performed in various conditions: in ethanol under reflux (method A) or in 10% sulfuric acid aqueous solution at 50 °C (method B). In the last case we could observe that when the 1,2-diamino-3-chloro-4-morpholinobenzene (**4a**) was condensed with the α-ketoesters **5e**, **5f** and **5h** under acidic conditions, we were able to obtain prevalently (**11a** > **10a**, **13a** > **12a** in 3:1 and 4:1 ratio, respectively) or exclusively (**17a**) the 7-morpholino derivatives than the 6-morpholino substituted-ones. These results seem to indicate that protonation of the amino group on the *meta* position to the morpholino group takes place thus forcing condensation of the *para* amino group with the ketocarbonyl group of the ester prior to ring closure. This behaviour was in part reversed in the case of the condensation of **4a** with **5g** to give **14a** > **15a** in a ratio of 3:2, whereas the steric hindrance of isopropyl group possibly promotes an inversion of reactivity of the ketocarbonyl group in comparison with that of the other α-ketoesters.

The different behaviour of reactivity of the examined diamine (**4a**) with the α-ketoesters in comparison with that previously observed in the case of 1,2-diamino-3-chloro-4-metoxybenzene [7] is probably due to the concomitant protonation of the morpholine nitrogen atom which makes less basic the amino group on the *para* position with respect to that in *meta* position.

Quinoxalines (**19a**–**c**) were prepared, according to the procedure reported by Huffman for the known (**19c**) [9], by condensation of the diamines **4a**–**c** with 1,4-dibromo-2,3-butanedione (**18**) in ethanol (Scheme 3).

Structures of all compounds synthesised have been supported by analytical and spectroscopical data (Elemental analyses and ^{1}H NMR) and were in agreement with those previously reported for similar compounds [4–7].

3. Experimental

3.1. Chemistry

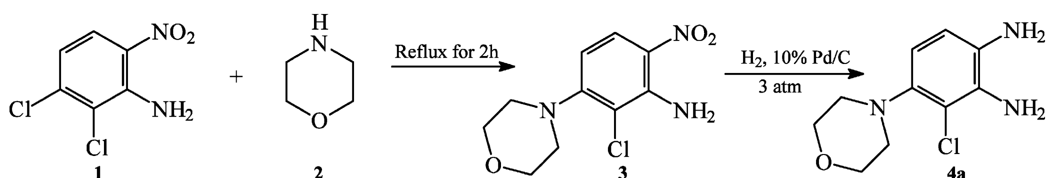
Melting points were determined by a Kofler hot stage or Digital Electrothermal apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Varian XL-200 (200 MHz) instrument, using TMS as internal standard. The chemical shift values are reported in parts per million (δ) and coupling constants (J) in Hertz (Hz). Signal multiplicities are represented by: s (singlet), d (doublet), t (triplet), q (quadruplet) and m (multiplet). Light petroleum refers to the fraction with b.p. 40–60 °C. Elemental analyses were performed by the Dipartimento di Chimica, Università di Sassari (Italy). The analytical results for C, H, N, were within ±0.4% of the theoretical values.

3.1.1. Intermediates

The diaminobenzene derivatives **4b**,**c** were commercially available, compound **4a** is a new derivative and its preparation is described below.

*3.1.1.1. Preparation of 2-chloro-3-morpholino-6-nitroaniline (**3**).* A mixture of 2 g (9.6 mmol) of 2,3-dichloro-6-nitroaniline (**1**), prepared as described [10], and 14.9 g (172 mmol) of morpholine was reacted under reflux for 2 h. On cooling, the reaction mixture was diluted with 100 ml of water. The precipitate formed was collected by filtration to give **3** in 90% yield as crystals, m.p. 142–143 °C (diethyl ether), ^{1}H NMR ($CDCl_3$): δ 8.00 (1H, d, J = 9.6 Hz, H-5), 6.72 (2H, s, NH_2), 6.24 (1H, d, J = 9.6 Hz, H-4), 3.88 (4H, t, J = 4.6 Hz, CH_2-3′+CH_2-5′), 3.19 (4H, t, J = 4.6 Hz, CH_2-2′+CH_2-6′). *Anal*. $C_{10}H_{12}ClN_3O_3$ (C, H, N).

*3.1.1.2. Preparation of 3-chloro-4-morpholino-1,2-diaminobenzene (**4a**).* Compound **3** (1.75 g, 6.8 mmol) in ethanol (100 ml) and in the presence of 10% palladium–charcoal (0.2 g) was hydrogenated under 3 atm until the uptake of the theoretical amount of hydrogen was reached. After filtration of the catalyst, the mother liquors were evaporated to dryness to give **4a** in 98% yield as a solid, m.p. 147–148 °C (diethyl ether), ^{1}H NMR ($CDCl_3$): δ 6.64 (2H, s, NH_2), 6.60 (1H, d, J = 8.2, H-6), 6.41 (2H, s, NH_2), 6.37 (1H, d, J = 8.2, H-5), 3.85 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 2.93 (4H, t,



Scheme 1. Preparation of the intermediate (**4a**).

Table 1
Analytical and spectroscopic data of compounds (**6**–**17** and **19**) obtained according to Schemes 2 and 3

Comp.	R	R_1	R_2	M.p. (°C)	Yield (%)	^{1}H NMR (solvent), δ (ppm), J (Hz)
6a		mor	H	239–240[a]	16 [a]	($CDCl_3$) 10.22 (1H, s, NH), 7.28 (1H, d, J = 9.2, H-8), 7.20 (1H, d, J = 9.2, H-7), 3.93 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.10 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 2.69 (3H, s, CH_3)
7a		mor	H	234–235	25 [a]	($CDCl_3$) 9.18 (1H, s, NH), 7.62 (1H, d, J = 8.8, H-5), 6.96 (1H, d, J = 8.8, H-6), 3.84 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.09 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 2.50 (3H, s, CH_3)
8a		mor	H	> 300	44 [a]	(DMSO-d_6) 12.69 (1H, s, NH), 7.49 (1H, d, J = 8.4, H-8), 7.25 (1H, d, J = 8.8, H-7), 4.62 (2H, s, CH_2Br), 3.76 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 2.98 (4H, t, J = 4.6, CH_2-2′+CH_2-6′)
8b		H	CF_3	219–220	84 [a]	($CDCl_3$+DMSO-d_6) 13.07 (1H, s, NH), 7.60 (1H, s, H-8), 7.57 (1H, s, H-6), 4.65 (2H, s, CH_2Br)
9b		H	CF_3	167–168	13 [a]	($CDCl_3$) 9.81 (1H, br s, NH), 8.09 (1H, s, H-5), 7.84 (1H, s, H-7), 4.64 (2H, s, CH_2Br)
10a		mor	H	277–278	15 [a], 14 [b]	($CDCl_3$+DMSO-d_6) 13.13 (1H, s, NH), 7.45 (1H, d, J = 9.0, H-8), 7.35 (1H, d, J = 9.0, H-7), 3.88 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.08 (4H, t, J = 4.6, CH_2-2′+CH_2-6′)
10b		H	CF_3	209–211	10 [a]	($CDCl_3$) 12.87 (1H, s, NH), 7.63 (1H, s, H-8), 7.56 (1H, s, H-6)
11a		mor	H	243–244	10 [a], 40 [b]	($CDCl_3$+DMSO-d_6) 11.75 (1H, s, NH), 7.81 (1H, d, J = 9.0, H-5), 7.11 (1H, d, J = 9.0, H-6), 3.87 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.25 (4H, t, J = 4.6, CH_2-2′+CH_2-6′)
12a		mor	H	252–254	18 [a], 7 [b]	($CDCl_3$) 12.05 (1H, s, NH), 7.21–719 (2H, m, H-7+H-8), 3.91 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.07 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 2.99 (2H, q, J = 7.4, CH_2), 1.38 (3H, t, J = 7.4, CH_3)
12b		H	CF_3	229–231	13 [a]	($CDCl_3$) 12.10 (1H, s, NH), 7.66 (1H, s, H-8), 7.50 (1H, s, H-6), 3.10 (2H, q, J = 7.4, CH_2), 1.43 (3H, t, J = 7.4, CH_3)
13a		mor	H	204–206	20 [a]30 [b]	($CDCl_3$) 9.71 (1H, s, NH), 7.71 (1H, d, J = 8.8, H-5), 7.03 (1H, d, J = 8.8, H-6), 3.90 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.16 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 2.95 (2H, q, J = 7.4, CH_2), 1.34 (3H, t, J = 7.4, CH_3)
13b		H	CF_3	173–174	23 [a]	($CDCl_3$) 9.76 (1H, s, NH), 8.06 (1H, s, H-5), 7.77 (1H, s, H-7), 3.01 (2H, q, J = 7.4, CH_2), 1.36 (3H, t, J = 7.4, CH_3)
14a		mor	H	233–234	12 [a]22 [b]	(DMSO-d_6) 12.45 (1H, s, NH), 7.48 (1H, d, J = 8.8, H-8), 7.29 (1H, d, J = 8.8, H-7), 3.84 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.60 (1H, m, CH), 3.05 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 1.31 (6H, d, J = 7.0, 2 CH_3)
14b		H	CF_3	242–244	23 [a]	($CDCl_3$+DMSO-d_6) 12.61 (1H, s, NH), 7.62 (1H, s, H-8), 7.52 (1H, s, H-6), 3.53 (1H, m, CH), 1.34 (6H, d, J = 6.8, 2 CH_3)
15a		mor	H	204–205	60 [a], 13 [b]	(DMSO-d_6) 11.84 (1H, s, NH), 7.87 (1H, d, J = 8.8, H-5), 7.29 (1H, d, J = 8.8, H-6), 3.85 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.66 (1H, m, CH), 3.25 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 1.37 (6H, d, J = 7.0, 2 CH_3)
15b		H	CF_3	160–162	29 [a]	($CDCl_3$) 9.32 (1H, s, NH), 8.07 (1H, s, H-5), 7.56 (1H, s, H-7), 3.62 (1H, m, CH), 1.33 (6H, d, J = 6.8, 2 CH_3)
16a		mor	H	171–172	34 [a], 0 [b]	($CDCl_3$) 12.85 (1H, s, NH), 7.40 (1H, d, J = 9.0, H-8), 7.30 (1H, d, J = 9.0, H-7), 4.55 (2H, q, J = 7.2, O-CH_2), 3.90 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.11 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 1.48 (3H, t, J = 7.2, CH_3)
16b		H	CF_3	168–170	23 [a]	($CDCl_3$) 12.73 (1H, s, NH), 7.72 (1H, s, H-8), 7.63 (1H, s, H-6), 4.57 (2H, q, J = 7.2, O-CH_2), 1.48 (3H, t, J = 7.2, CH_3)
17a		mor	H	180–181	22 [a], 58 [b]	($CDCl_3$) 9.54 (1H, s, NH), 7.85 (1H, d, J = 9.0, H-5), 7.07 (1H, d, J = 9.0, H-6), 4.51 (2H, q, J = 7.2, O-CH_2), 3.92 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.25 (4H, t, J = 4.6, CH_2-2′+CH_2-6′), 1.45 (3H, t, J = 7.2, CH_3)
19a	Cl	mor	H	110–112	73	($CDCl_3$+DMSO-d_6) 7.96 (1H, d, J = 9.2, H-8), 7.61 (1H, d, J = 9.2, H-7), 4.97 (2H, s, CH_2Br), 4.93 (2H, s, CH_2Br), 3.96 (4H, t, J = 4.6, CH_2-3′+CH_2-5′), 3.30 (4H, t, J = 4.6, CH_2-2′+CH_2-6′)
19b	Cl	H	CF_3	78–80	92	($CDCl_3$) 8.31 (1H, s, H-8), 8.06 (1H, s, H-6), 5.00 (2H, s, CH_2Br), 4.96 (2H, s, CH_2Br)

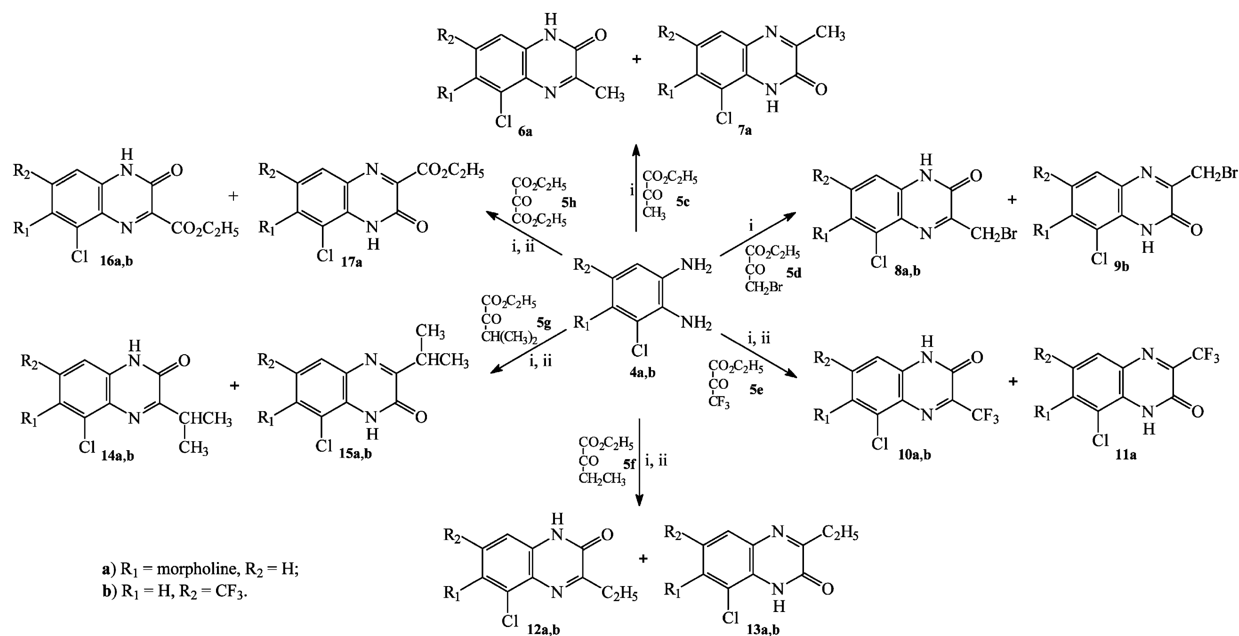
Mor, Morpholine.
[a] Yield of method A.
[b] Yield of method B.

J = 4.6, CH_2-2′+CH_2-6′). *Anal*. $C_{10}H_{14}ClN_3O$ (C, H, N).

3.1.2. General procedure for preparation of quinoxalinones ***6a**, **7a**, **8a**–**b**, **9b**, **10a**–**b**, **11a**, **12a**–**b**, **13a**–**b**, **14a**–**b**, **15a**–**b**, **16a**–**b** and **17a***

3.1.2.1. Method A. A solution of equimolar amounts (3.0–4.0 mmol) of the appropriate diamines **4a**–**b** and the suitable α-ketoesters **5d**–**h**, and **4a** with **5c**, in ethanol (20 ml) was stirred and refluxed for 2 h in the case of **6a**, **7a**, **8a**–**b**, **9b**, **10a**, **11a**, **12a**–**b**, **13a**–**b**, **14a**, **15a**, **16a**–**b**, **17a**, for 48 and 10 h for **10b** and for the mixture **14b**/**15b**, respectively.

After evaporation of the solvent, a residue was chromatographed on silica gel column, eluting with a 8:2 mixture of diethyl ether/light petroleum, in order to separate the mixture of isomers when present. In any



Scheme 2. Preparation of quinoxalin-2-ones **6a**, **7a**, **8a**–**b**, **9b**, **10a**–**b**, **11a**, **12a**–**b**, **13a**–**b**, **14a**–**b**, **15a**–**b**, **16a**–**b** and **17a**. Conditions: (i) EtOH, under reflux for 2–48 h; (ii) H_2SO_4 10% aqueous solution at room temperature or 50 °C for 1 h.

case we observed that the 8-chloro derivatives move faster in the eluate than the 5 substituted-ones. In Table 1 we report the structures, melting points, yields, and ^{1}H NMR data of all compounds synthesised.

3.1.2.2. Method B. A mixture of equimolar amounts (3.5 mmol) of **4a** and the suitable α-ketoester (**5e**–**h**) in 10% sulfuric acid aqueous solution (20 ml) was stirred at 50 °C for 1 h in the case of **10a**, **11a**, **12a**, **13a**, **14a** and **15a**, or at room temperature for **16a** and **17a**. On cooling to room temperature from the reaction mixture a crude precipitate was formed and collected by filtration. Purification by chromatography on silica gel column was carried out, eluting with a mixture of solvents as reported above.

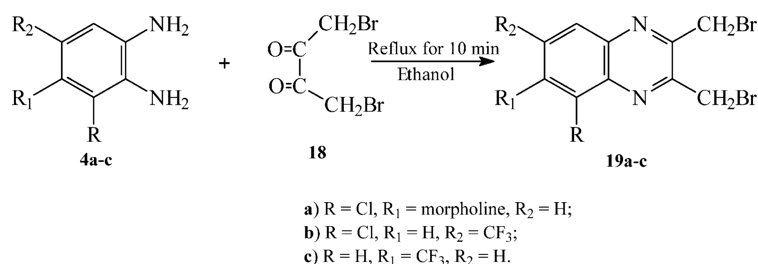
*3.1.3. General procedure for preparation of 2,3-bis(bromomethyl)quinoxalines **19a**–**c***

A solution of equimolar amounts (2.5 mmol) of the appropriate diamine (**4a**–**c**) and 1,4-dibromo-2,3-butanedione (**18**) in ethanol (15 ml) was refluxed for 10 min and then diluted with 100 ml of water. The crude precipitate formed was purified by chromatography on silica gel column, eluting with a 7:3 mixture of diethyl ether/light petroleum. Melting points, yields, and ^{1}H NMR data are reported in Table 1.

3.2. Microbiology

3.2.1. Antibacterial assay

Antibacterial activity was investigated in vitro on Gram positive and Gram negative bacteria. The strains used in these tests were from American Type Culture Collection (ATCC): *S. aureus* ATCC 25923, *E. coli* ATCC 3853, *Klebsiella pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853, or were environmental isolate (*Vibrio alginolyticus*). A logarithmic phase culture of each bacterial strain was diluted with Luria broth in order to obtain a density of 10^6 CFU/ml. The test was performed in a 96 well microtiter plate in a final volume of 100 µl. Test compounds were dissolved in dimethyl sulfoxide at an initial concentration of 1000 µg/ml and serially diluted in the plate (500–7.8 µg/ml) using Luria broth. Each well was then inoculated with the standar-



a) R = Cl, R_1 = morpholine, R_2 = H;
b) R = Cl, R_1 = H, R_2 = CF_3;
c) R = H, R_1 = CF_3, R_2 = H.

Scheme 3. Preparation of quinoxalines (**19a**–**c**).

dised bacterial suspension and incubated at 37 °C for 18–24 h. One well containing bacteria without sample (growth control), and one well containing broth only (sterility control) were also used. After the incubation, the growth (or its lack) of the bacteria was determined visually in both containing compound well sand control well. The lowest concentration at which there was no visible growth (turbidity) was taken as the MIC. In addition 5 μl of suspension from each well were inoculated in a Muller Hinton agar plate to control bacterial viability.

3.2.2. Antimycotic assay

Antifungal activity was determined by the tube dilution method on clinical isolates of *Candida* spp. Yeast inocula were obtained by properly diluting cultures, previously incubated at 35 °C for 48 h in Sabouraud Dextran agar, to obtain a density of 10^6 CFU/ml. Test compounds were dissolved in dimethyl sulfoxide at an initial concentration of 1000 μg/ml and then were serially diluted in culture medium to 15.6 μg/ml. Then, 0.5 ml of the above serial dilutions of test compounds were added, in sterile polystyrene tubes, with an equal volume of fungal suspension and incubated at 35 °C for 48 h. The MIC determination was performed in duplicate, and defined as the lowest concentration of the compound which produced no visible growth. A sample of compound free growth control and a set of tubes with sample alone for monitoring contamination of the medium were used.

4. Results and discussion

Quinoxalinones **6a**, **7a**, **8a**–**b**, **9b**, **10a**–**b**, **11a**, **12a**–**b**, **13a**–**b**, **14a**–**b**, **15a**–**b**, **16a**–**b** and **17a** and quinoxalines (**19a**–**c**) were evaluated in vitro for antibacterial (*S. aureus*, *E. coli*, *V. alginolyticus*, *K. pneumoniae* and *P. aeruginosa*), and antifungal (*Candida* spp) activities.

With regard to antibacterial activity, the obtained results mainly indicate that most of tested compounds exhibited moderate activity against Gram positive and Gram negative bacteria showing MIC values ranging from 125 to 500 μg/ml with a few exceptions. Compounds **9b**, **14b** and **19b** (MIC = 62.5 μg/ml) and **10b** (MIC = 15.6 μg/ml) were the most active against *V. alginolyticus*, compared with ciprofloxacin (MIC = 0.5 μg/ml).

The result of in vitro anticandida activity shows that none of the tested compounds exhibited a significant activity (MIC $\geq$ 250 μg/ml).

Despite our previous results recorded on the compounds bearing a single substituent at C-6 or C-7 of the quinoxaline ring [4–7], the data obtained from the actual screening allow us to make the following observations. The concomitant presence of a CF_3 group with a chlorine atom on the benzo-moiety associated with the substituent at C-3 position as CH_2Br, CF_3, or C_3H_7 groups in quinoxalinone derivatives, in general seem to induce a lower activity against bacteria and *Candida* spp. whilst promoting a better activity against *V. alginolyticus*. Analogous behaviour was observed in the series of quinoxalines having identical substituted ring counterpart and two CH_2Br groups in both C-2 and C-3. The presence of a chlorine atom associated with morpholine in the benzene moiety makes the quinoxalinone derivatives completely inactive.

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